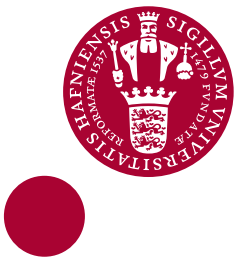

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"What's wrong with my monkey?" Ethical perspectives on germline transgenesis in marmosets[1]

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Abstract

The birth of the first transgenic primate to have inherited a transgene from its parents opens the possibility to set up transgenic marmoset colonies, as these monkeys are small and relatively easy to keep and breed in research facilities. The prospect of transgenic marmoset models of human disease, readily available in the way that transgenic laboratory mice are currently, prompts excitement in the scientific community; but the idea of monkeys being bred to carry diseases is also contentious. We structure an ethical analysis of the transgenic marmoset case around three questions: whether it is acceptable to use animals as models of human disease; whether it is acceptable to genetically modify animals; and whether these animals' being monkeys makes a difference.

The analysis considers the prospect of transgenic marmoset studies coming to replace transgenic mouse studies and lesion studies in marmosets in some areas of research. The mainstream, broadly utilitarian view of animal research suggests that such a transition will not give rise to greater ethical problems than those presently faced. It can be argued that using marmosets rather than mice will not result in more animal suffering, and that the benefits of research will improve with a move to a species more similar in phylogenetic terms to humans. The biological and social proximity of monkeys and humans may also benefit the animals by making it easier for scientists and caretakers to recognize signs of suffering and increasing the human motivation to limit it. The animal welfare and research impacts of the transition to marmoset use will depend very much on the extent to which researchers take these issues seriously and seek to minimize animal harm and optimize human benefit.

Keywords: Ethics; Refinement, Harm-benefit, Disease model; Non-human primate

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Introduction

In May this year, Sasaki and co-workers (2009) announced the birth of the first monkey to have inherited a vector-integrated transgene from its parents. The event attracted media attention, although in fact it is not the first time that a transgenic primate has been engineered. The first genetically modified monkey, a rhesus macaque named ANDi, was unveiled eight years ago (Chan et al 2001) and received huge international media coverage.

The reasons for the enthusiasm over the monkey born this year are three: it carries a transgene inherited from its genetically modified parents; the parents were modified by means of a so-called 'viral vector'; and the monkey was a marmoset. The potential for successful large-scale germline transmission in this small primate, which breeds well in captivity, may be such that self-sustaining colonies of transgenic animals can be set up.

The prospect of transgenic marmoset models of human disease, readily available in the way that laboratory mice are currently, prompts excitement in the scientific community. However, the idea of monkeys being bred to carry diseases is also contentious. In the present Perspective paper we present an ethical analysis of the transgenic marmoset case. We discuss three questions: whether it is acceptable to use animals as models of human disease; whether it is acceptable to genetically modify animals; and whether these animals' being monkeys makes a difference.

Transgenic marmosets in research – technical prospects

The analysis is based on two key assumptions about the implications of the recently published results.

First, we assume that the results presented by Sasaki et al (2009) are repeatable, and that further technological developments will enable colonies of transgenic marmosets to be produced. There are some technical hurdles to overcome, but there is no reason to suspect that these will prove insuperable.

Second, we assume that the monkeys produced will carry human disease mutations. For practical reasons, given their much slower reproduction rate, marmosets are highly unlikely to replace mice as the mammal of choice for gene function studies. Instead, transgenic marmoset disease models are expected to replace mice in some biomedical research. This is likely to happen particularly in areas where marmosets are already used, such as reproductive biology, infectious disease, and behavioural and neuroscience research (Mansfield 2003).

Transgenic marmosets in research – the ethical issues

We will argue, there are three main ethical issues at stake in the transgenic marmoset case. These can all be summarized in one sentence: it is a question of *monkeys* being *genetically modified* in order to *develop diseases.* We will discuss these issues in reverse order.

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Is it ethically acceptable in the name of medical research to induce diseases in animals?

The use of animals in research is controversial. The main concern is that living, sentient beings are deliberately caused to suffer from diseases which may be painful and which we, as humans, seek to avoid. It is not self-evident that we have the right to use animals in this way. On the other hand, failure to conduct research that can generate important knowledge, and which may in some cases be the only way to answer questions crucial to the development of treatment for serious human diseases, is ethically costly too.

The mainstream view of animal use in research has a strong utilitarian component. Animal ethics or animal use committees are expected to perform harm-benefit analyses in which they weigh any expected harm to research animals against the potential benefits of the study. In practice, however, the analysis departs from uncompromising utilitarianism in that different species prompt rather different considerations and human interests are given priority.

Formal discussion of ethical issues in animal research has traditionally focused on how to minimize animal harm through the principle of the 3Rs: replacement, reduction, and refinement (Russell and Burch 1959). We shall focus on refinement.

Refinement to minimize animal suffering covers the way animals are housed and handled in general; how substances are administered and samples are collected; how diseases are induced, and to what level of severity they are allowed to proceed; and how animals are euthanized at the end of an experiment. Laboratory animal science as a discipline has addressed this issue for a couple of decades, and considerable progress has been made in the development of more refined approaches. Likewise, the fact that an increasing number of countries apply extensive scrutiny to animal research protocols before approval indicates an increasing attention to harm reduction – even though geographic and cultural variation as well as economic constraints may limit the extent to which measures of refinements are actually applied.

Nevertheless, recent work shows that even approved and published research involving potentially high levels of animal distress may fail to apply refinement properly, both as regards adoption of housing refinement and the imposition of humane endpoints to animals with severe motor incapacity (Olsson et al 2007, 2008), and the use of postoperative analgesia in animals subjected to surgical interventions (Richardson and Flecknell 2005).

Scientific benefits are, of course, equally important: after all they are the reason animals are used in research. Scientists typically appeal to the benefits of animal experiments in general terms, referring to successful applications in the past; and animal ethics committees have little room for more than a general evaluation of whether the research question is relevant and the approach to it reasonable. More specific discussion, within different areas of research, of what characterizes a good animal experiment and a good animal model is largely absent in the biomedical research literature (but see Markou et al 2009 for a recent, detailed review).

Discussion of this latter kind is now urgent. Recently published systematic reviews and meta-analyses reveal that many studies use suboptimal design and methodology, and that this may at least partly explain the poor correspondence of results in preclinical animal research and subsequent human clinical trials. Typically, treatment effects are overestimated in studies in which animals are not randomized over treatments and where researchers inducing lesions and assessing outcomes are not blinded to the animals' treatment group membership (e.g. Sena et al 2007).

The ethical acceptability of animal experiments requires a positive balance of harm and benefit to be struck. People are more supportive of animal use in research if there is a clear human health benefit, and become less supportive as animal harm intensifies (Aldhous et al. 1999). Therefore, it is an ongoing challenge for science and society to ensure the greatest possible benefit and the smallest possible harm to animals. Fundamental research which in retrospect often turns out to deliver important results poses a special problem for prospective assessments of potential benefits.

It should be borne in mind that the analysis in this section has been undertaken primarily from a mainstream, broadly utilitarian view, and that not everyone takes this view. Animal rights and feminist ethics, for example, typically criticize animal models primarily on the grounds that they violate the rights of and exploit animals (Shapiro 1998; Sandøe and Christiansen 2008).

However, many critics of animal use take a very pragmatic stance. They accept the harm-benefit framework but question how much of the apparent progress is genuine and how much rather reflects an increased ability of members of the research community to say the right words and communicate a positive message. It is therefore important that efforts are made by the research community to genuinely limit harm and optimize benefit.

The challenge to improve the harm-benefit balance applies to the transgenic marmoset case in the exactly same way as it does to any other use of animals in research. However, other issues may be different in the marmoset case, as we shall now see.

Is it ethically acceptable to genetically modify animals?

Biotechnologies that involve the genetic manipulation of higher organisms (animals rather than plants or microorganisms) seem to evoke particularly strong public concerns (Lassen et al. 2006). Bioethicists have coined the phrase ‘animal integrity’ to express one such concern. The basic idea is that we should not alter the ‘normal’ genetic profiles of animal species (Gjerris et al 2006).

This idea seems to assume that animals have a relatively fixed genetically defined nature, and that human interference with this is morally (or perhaps aesthetically: it is sometimes hard to tell what is at stake) objectionable. And this idea may, of course, be questioned.

Some people will argue that as long as the animals involved will not be caused to suffer low levels of welfare there is no problem about changing animals genetically. However, these people may also wish to stress the need for *precaution* in this area. In practice it is difficult to foresee effects on modified animals accurately. Those who are essentially pro-modification may therefore interpret the idea of animal integrity as a precautionary attitude to rapid and radical animal modifications.

Others may believe that although alterations of animals through, for example, breeding are inevitable, there is a limit to how far we, as humans, may go in changing our fellow creatures. This view may be based on the ethical claim that we should respect nature in its own right (Sandøe and Christiansen 2008, Ch. 9), and applies to modern biotechnologies as well as more traditional techniques such as selective breeding.

Compared with the other methods that could be applied to create animal-based disease models, an approach involving genetic manipulation and the erosion of genetic integrity may anyway be seen as a lesser evil. In

the marmoset case, 'disease models' are already generated by inducing lesions in healthy animals, so that these come to recapitulate aspects of the disease (Mansfield 2003; Vitale et al 2009).

Does it make a difference that the animals are monkeys?

Experimental use of non-human primates is more controversial than any other research involving animals. That is, people are generally more concerned about research employing primates than they are about similar work involving other mammals (Aldhous et al 1999). The issue here is the proximity between humans and other primates.

This proximity is not only phylogenetic, for it can also be understood in the light of the so-called the socio-zoological scale (Arluke and Sanders 1996). This scale rates animals in terms of how greatly they are valued by humans. Companion animal species and non-human primates presently top the scale in the Western World.

From a harm perspective, species may be important in that species characteristics determine animals' capacity to suffer and our possibility to house and handle them appropriately. Regarding suffering, the capacity to have negative subjective experiences such as pain or fear, and the capacity for self-awareness seem particularly important. While the former seems to be present in all mammals (Smith and Boyd 1991), it is unclear if animals other than great apes and some cetaceans possess the latter (Byrne 2000; Reiss and Marino 2001). Regarding housing and handling, the fact that primate species are not fully domesticated and the lack of self-sustaining breeding colonies for several species give rise to specific concern about the welfare in particular of wild-caught animals.

From this perspective, marmosets pose less of a problem than Old World Monkeys like macaques. Breeding well in captivity outside their native country (Brazil), marmoset colonies can be established in user countries; this eliminates the animal welfare problems with wild capture of breeding animals and the intercontinental transportation of research animals (Mansfield 2003). The provision of good housing for marmosets is still considered easier than for macaques (Smith et al 2001), although marmosets' natural behaviour as tree-dwelling animals does present housing challenges in terms of vertical space (Jennings and Prescott 2009).

There are respects in which primates may be better off than, for example, rodents. In handling primates and training them to cooperate with experimental and husbandry procedures it is common to use positive reinforcement rather than relying on physical restraint (Prescott and Buchanan-Smith 2007). The actual and perceived closeness of the relationship between primates and humans might also encourage researchers to treat primates well.

Phylogenetic proximity also affects the expected benefits of research. Although marmosets are relatively distant kin of ours within the order Primates, they are still genetically much more closely related to humans than any non-primate species used in research. This is particularly relevant when results are extrapolated between species, as happens in preclinical research and safety testing – areas where the marmoset use is advocated for on the basis of phylogenetic proximity, small body size, and ease of breeding and keeping (Mansfield 2003).

Rather different ethical concerns are prompted by the development of transgene technologies in primates. The ability to induce heritable changes to the germline DNA of other primate species will bring us

technologically closer to human genetic engineering, and some see this as a dangerous slippery slope to human transgenesis (Schatten and Mitalipov 2009). Exploring that concern further is beyond the scope of the present paper, but the reader interested in a philosophical analysis of the plausibility of the slippery-slope argument is referred to Holtug (1993).

Discussion

We have considered the possibility of transgenic marmoset studies coming to replace transgenic mouse studies and lesion studies in marmosets in some areas of research. The mainstream, broadly utilitarian view of animal research suggests that such a transition will not give rise to more serious ethical problems than we face at present.

It can be argued that marmoset use, as opposed to mouse use, will not worsen animal suffering, and that research benefits flow from any move to a more phylogenetically similar species. One may even speculate that biological and social proximity of laboratory animals and human experimenters may benefit the animals at least in cultural settings where there is already raised awareness of animal welfare issues. First, it may make it easier to recognize signs of suffering. Second, motivation to limit suffering may be higher if animals are marmosets than if they are mice.

Clearly, the animal welfare and research impacts here will depend very much on the extent to which researchers take these issues seriously and seek to minimize animal harm and optimize benefit both for human health and for animal health and conservation.

There is a widespread perception that primates are special in a *symbolic* way. Scientists are sometimes uncomfortable with the notion that this really matters morally. They often prefer to discuss the special status of primates in terms of neuro-physiological capacities. Thus the ESF-EMRC expert group states: “Whether or not a species needs special protection should not be based solely on its phylogenetic relations to humans, but on its potential for suffering. NHPs [non-human primates] are distinguished by the very advanced nature of their social, cognitive, sensory and motor functions” (ESF-EMRC 2009).

The biological characteristics of some laboratory primates will sometimes cause them to suffer more than dogs or rodents – for example, because they are more difficult to house or need to be transported over long distances, or because they possess self-reflective capacities. These worries do not apply to marmosets.

Nevertheless, there is reason to take the socio-zoological scale seriously. First, it also influences scientists’ reactions: affective relation was considered the most important factor in determining the ethical acceptability of using animals of a particular species in research among scientists participating in laboratory animal science training (own unpublished data). Second, given public sensitivities, there is concern that increased focus on transgenic primate research could play into the hands of activists and ultimately lead to increased public resistance to animal research as such.

As the authors of the Nature editorial (2009) accompanying publication of the research paper recognize, research of the kind discussed here challenges researchers to face the public and explain their work. To do this in a credible way, researchers need to be able to show that they take refinement and translational considerations seriously. This demands more than simply asserting that animals do not suffer much and that research is beneficial – it requires being able to explain and demonstrate how this is achieved.

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